REMARKS

Claims 15-34 and 53-72 are pending in the present application. Claims 15, 53, 65, 68 and 72 and been amended without prejudice and without acquiescence, and claims 16, 18-19, 54, 56-57 have been canceled without prejudice and without acquiescence. Claims 1-14, 39-52, 73-92 have been canceled without prejudice and without acquiescence as these claims are drawn to a non-elected invention. Claims 17 and 55 have been canceled without prejudice and without acquiescence as these claims are drawn to a non-elected species. Applicants retain the right to file a divisional application to any cancelled or nonelected claims. Applicants' species election is made without prejudice or acquiescence. Upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species, provided that all claims to each additional species are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.146. No new matter has been added.

The issues outstanding in this application are as follows:

- The Specification is objected to as allegedly containing hyperlinks.
- Claims 15, 16, 18-34, 53, 54, 56-72 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described.
- Claims 15, 16, 18-34, 53, 54, 56-72 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.
- Claims 15, 16, 18, 27, 34, 53, 54, 56, 65, and 72 were rejected under 35 U.S.C. § 102(b) as being anticipated by Antonsson et al. (WO 97/36932).

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. Specification

The specification has been amended and contains no informalities. No new matter has been added.

II. 35 U.S.C. § 112, first paragraph

Claims 15, 16, 18-34, 53, 54, and 56-75 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification such a way as to enable one of skill in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse.

The Action states that the specification fails to provide written description of the specific structure of SEE as corresponding to the functional regions of A-E. Applicants traverse.

In order to advance the prosecution of the application, applicants have amended claims 15 and 53 without prejudice and without acquiescence. The independent claims clearly describe and enable mutations within regions A-E. Regions A-E of the present invention are regions that contain antibody binding sites as shown in Figures 1, 2, 4, and 5. More specifically, Figure 4 clearly illustrates a sequence alignment of SEA, SEE, SEA/E-18 and SEA/E-120 along with the regions A-E, which are defined as the lines above the sequences and labeled A-E. Thus, the sequence of SEE and the corresponding regions of A-E are described in the specification. Since the sequence of SEE and the corresponding regions of A-E are described in the specification, Applicants assert that one of skill in the art would be able to make substitutions in any of the various regions of A-E using standard molecular biological techniques and protein chemistry, for example see specification paragraphs [0060]-[0098], which discuss general methods of amino acid substitutions and site-specific mutagenesis. Still further, Table 1, and Figures 7, 8A and 8B, provide examples of chimeric molecules having mutations in the identified regions of Figure 4 or which show reduced seroreactivity. Thus, Applicants assert that the specification meets the enablement requirement.

The Action further states that the specification is devoid of written description of how to make and use a tri-partite conjugate. Applicants traverse.

The specification teaches that the cytokine can be conjugated or it can be administered as an adjuvant (*See* paragraph [0104]). The specification also discusses general methods of fusion proteins (*See* paragraph [0068]). Applicants assert that techniques of producing fusion proteins are well known by those of skill in the art. More specifically, PCT publication WO99/04820 teaches the methodology of how to make a tri-partite conjugate as well as the benefit of a tri-partite conjugate for reducing the amount of tumors. Applicants remind the Examiner that as a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). In view of the description in the present application and the knowledge in the art, Applicants assert that the written description requirement has been meet.

Still further, the Action on page 8 states SEE and variants thereof have a markedly reduced ability as compared to SEA to induce T cell proliferation. The cited basis for this rejection is Cavallin et al., page 1671 column 1. Applicants traverse.

Applicants believe that the Examiner has misconstrued the Cavallin reference. EC_{50} is defined as the concentration giving 50% of maximal effect (*See* Antonsson et al., *J. Immunol.* 158:4246, 1997). The lower the EC_{50} value, the lower the concentration of the substance to result in the same response. Thus, as shown in Table 1 of Cavallin et al., SEE and variants thereof require a lower concentration to result in the same response. More importantly, page 1671 column 1 of Cavallin et al. teaches that SEA has three times lower proliferation activity than SEE as determined by EC_{50} values. Thus, Applicants assert that Cavallin et al. teaches that SEE and variants thereof are more potent than SEA.

The Action on page 9 also states that Weinrauch et al. teaches that only SEA and SEB have demonstrated cell death *in vivo* and thus one of skill in the art would doubt that conjugates of SEE would be used as a therapeutic treatment of cancer. Applicants traverse.

Applicants believe that the Examiner has misconstrued the Weinrauch reference. Weinrauch describes the ability of superantigens to induce cell death or apoptosis in T cells. This phenomenon is not related to the anti-tumor effect of superantigens; in fact, it is the complete opposite. The anti-tumor effect of the superantigen conjugates of the present

invention results in initiation of a T-cell attack against the tumor cells by increasing T-cell proliferation and activity; not destruction of the T-cells. Thus, Applicants assert that one of skill in the art would not relate the teachings of Weinrauch to the present invention since the teachings of Weinrauch et al. result in the complete opposite effect of the present invention.

The Action also states that the specification is devoid of data correlating *in vitro* data to *in vivo*. Applicants traverse.

Evidence of pharmacological or other biological activity of a compound is relevant to an asserted therapeutic use if there is reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980).

Paragraph [0160] of the specification states that the SEA/E-18 chimera retained an efficient level of cytotoxicity as in SEA. Since SEA has been demonstrated to induce cell death *in vivo* (as stated by the Examiner on page 9 of the Office Action), one of skill in the art would form the correlation that the SEA/E-18 chimera would also induce cell death *in vivo* similar to SEA since it retained cytotoxicity similar to SEA. Still further, the specification provides other chimeras that resulted from substitutions of SEA/E-18 (*See* paragraphs [0159] to [0176] and table 1) in which these chimeras also showed biological activity similar to SEA (*See* Figures 7, 8A and 8B). Thus, Applicants contend that the biological activity that is provided in the specification is a reasonable correlation that the SEE conjugates will have the asserted utility of a cancer therapeutic.

In further support of the present invention and on the relevence of 5T4 in NSCLC therapy, applicants enclose herewith a recent publication by the inventors demonstrating the *in vivo* cytotoxicity using the conjugate 5T4FabV13-SEA_{D227A} (*See* Forsberg et al., *British Journal of Cancer*, 85:129-136, 2001). Figure 5 of the Forsberg reference shows that intravenous treatment of 5T4FabV13-SEA_{D227A} to a mouse model for non-small-cell lung cancer (NSCLC) resulted in more than 85% reduction in the number of tumors and more than 95% reduction in tumor mass.

In view of the above arguments, Applicants have described and enabled the invention as claimed and respectfully request that the rejection be withdrawn.

III. 35 U.S.C. § 112, second paragraph

Claims 15, 16, 18-34, 53, 54, and 56-75 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants respectfully traverse.

A. Region C, Region A and Region E

Claims 15, 16, 18-34, 53, 54, and 56-75 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Action states that the claims are indefinite from the use of the terminology Region C, Region A and Region E because neither the specification nor the claims define these regions on any enterotoxin. Applicants traverse.

Figure 4 clearly illustrates a sequence alignment of SEA, SEE, SEA/E-18 and SEA/E-120 along with the regions A-E, which are defined as the lines above the sequences and labeled A-E. Thus, the sequence of SEE and the corresponding regions of A-E are described in the Specification. Applicants respectfully request that the rejection be withdrawn.

B. The term "low"

Claims 15, 16, 18-34, 53, 54, and 56-75 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Action states that the term "low" is indefinite. Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended independent claims 15 and 53 to clarify the present invention without prejudice and without acquiescence. In light of this amendment, Applicants respectfully request that the rejections be withdrawn.

C. Sequence identifier

Claims 19, 21, 23-25, 57, 59 and 61-63 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Action states the claims are indefinite in the recitation of particular residue positions in the absence of any corresponding sequence identifier. Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended independent claims 15 and 53 to clarify the present invention by the incorporation of a sequence identifier without prejudice and without acquiescence. In light of this amendment, Applicants respectfully request that the rejections be withdrawn.

IV. 35 U.S.C. § 102(b)

Claims 15, 16, 18, 27, 34, 53, 54, 56, 65, and 72 are rejected under 35 U.S.C. § 102(b) as being anticipated by Antonsson et al. (WO 97/36932). The Action states that Antonsson et al. teaches multiple SEE/A chimerics fused toC215FAb. Applicants respectfully traverse.

In order to advance the prosecution of the present application, Applicants have amended independent claims 15 and 53 to contain the limitation of dependent claims 19 and 57 without prejudice and without acquiescence. Claims 19 and 57 are not anticipated by Antonsson et al. Thus, the incorporation of the subject matter of claims 19 and 57 into independent claims 15 and 53 makes this rejection moot and Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. According, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02188US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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